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CITATION:

Ito, Noriyuki ...[et al]. Outcomes of curative nephrectomy against renal cell carcinoma based on a central pathological review of 914 specimens from the era of cytokine treatment.. International journal of clinical oncology 2015, 20(6): 1161-1170

ISSUE DATE:

2015-12

URL:

http://hdl.handle.net/2433/209709

Outcomes of curative nephrectomy against renal cell carcinoma based on a central pathological review of 914 specimens in the era of cytokine treatment

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This manuscript includes 250 words in the abstract, 2803 words in the manuscript, 4 tables, and 6 figures.

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ABSTRACT

Background

This study aimed to demonstrate the state of modern practice with regard to renal cell carcinoma (RCC) outcomes and to assess the impacts of clinical and pathological factors such as histological subtype (HS) or nuclear grade on survival using a central pathological review based on current the World Health Organization classification and American Joint Committee on Cancer/Union for International Cancer Control staging system.

Methods

We collected glass slides and clinical data sets from 914 cases of RCC treated with curative nephrectomy from 1995 to 2000. Overall (OS), cancer-specific (CSS), and relapse-free survival (RFS) were compared with HS and nuclear grades determined by a central pathology review board comprising 5 board-certified pathologists, pathological staging, and various clinical factors.

Results

The 5- and 7-year CSS in the present study were 96% and 93%, respectively, and were superior to those reported in Western countries. The concordance rates between the original and reviewed HS and nuclear grades were 90.9 % and 21.1 %, respectively. HS correlated with OS (P = 0.043) but was not an independent prognostic factor in the multivariate analysis (P = 0.820). Tumor size, Fuhrman grade and infiltration type were common independent prognostic factors of OS, CSS, and RFS.

Conclusions

The current study represents the state of RCC outcomes in the era of cytokine treatment for metastasis. Central pathological review is an essential component of a multicenter study with long-term follow-up. Tumor size, Fuhrman grade, and infiltration type had much greater impacts on survival after curative nephrectomy than did HS.

KEY WORDS:
central pathology, cytokine, histological subtypes, prognostic factors, renal cell carcinoma

Introduction

The incidence of renal cell carcinoma (RCC) is increasing; RCC accounts for approximately 3% of all cancers among adults in Western countries, and its incidence is also increasing in Japan [1]. Although tumor staging (TNM), Fuhrman grade, and performance status (PS) are the most widely recognized prognostic factors for RCC, easily available prognostic parameters that facilitate patient management based on different mortality risks have been investigated [2]. Consequently, various nomograms and scoring algorithms have been proposed, although in most series data were collected over more than a decade without sufficient follow-up. In addition, few studies have included a central pathological review based on the current World Health Organization (WHO) classification (2004) [3] and the seventh edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system, which was published in 2009[4]. Therefore, information from those earlier studies cannot be applied to current patient management. Also, it remains uncertain whether the histological subtype (HS) is an independent prognostic factor for RCC. To the best of our knowledge, only 5 studies have investigated the prognostic impact

of HS through pathological review [5-9], and single pathologists performed pathological reviews in 4 of these studies. Furthermore, to demonstrate the state of modern practice with regard to RCC outcomes, a multi-institutional study of patient data collected during a short period is mandatory. Therefore, in this study we attempted to collect data from 914 cases of RCC treated with potentially curative nephrectomy at 22 centers during a short period (6 years) and investigated the impacts of anatomical and clinical factors, HS, and nuclear grades on survival using a central pathological review by 5 board-certified pathologists who specialized in renal neoplasm.

Patients and Methods

Patients

We collected data from patients with histopathological diagnoses of RCC during original pathological evaluations at 22 urological centers in Japan between 1995 and 2000. To determine the exact situation regarding the outcomes of patients with RCC in 2000, we limited the data collection period to a relatively short duration of 6 years. The patients' clinical records were extracted from each institutional database. Each center was requested to

conduct a follow-up mail or telephone survey to obtain survival data for more than 85% of patients with RCC at 5 years post-diagnosis. Collected data included the TNM stage (AJCC/UICC, seventh edition), original histopathological diagnosis made at each institution, PS, overall survival (OS), cancer-specific survival (CSS), relapse-free survival (RFS), clinical symptoms, and laboratory test results. Data were labeled at the respective institutions and pooled into a single database.

Pathological evaluation

To evaluate case eligibility for this study, 2 representative hematoxylin and eosin (H&E) slides from each case were requested for a central pathological review. The review board comprised 5 board-certified diagnostic pathologists specializing in urologic pathology, including 1 author (YM). Each pathologist assigned their interpretations according to the Heidelberg classification of renal cell carcinoma (UICC Workshop 1997) [10], the WHO classification (2004), and nuclear grade according to the Fuhrman system and Japanese classification [11]. In addition, papillary subtype was divided into 2 categories, types 1 and 2 papillary RCC. Cases with discordant

interpretations were reevaluated to obtain consensus on the HS and grade through pathology review committee meetings. The presence of coagulative tumor necrosis could not be evaluated because only 2 representative slides were available for review.

Statistical analysis

OS, CSS, and RFS curves were calculated according to the Kaplan–Meier method. The log-rank test was used to evaluate the effects of patients' characteristics on OS, CSS, and RFS. To identify independent prognostic factors, we performed a Cox proportional hazards regression analysis with a backward elimination. A kappa statistic was used to measure the agreement between the initial diagnosis and central pathology review. All statistical analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA), and a 2-sided P-value of <0.05 was considered statistically significant.

Results

Patient population

A total of 914 cases of RCC treated with potentially curative nephrectomy (788 radical and 126 partial) against local tumors were collected; of these, 119 patients (13.0%) developed recurrent disease. The median follow-up period for the 782 surviving patients was 89 months, and the median survival duration was 47 months for the 132 patients who died during follow-up. Five cases (0.48%) died within 1 month of nephrectomy as a result of complications or rapid RCC progression in advanced cases, and 27 cases (6.3%) of pT1a, cN0M0 RCC (n = 431) recurred after curative nephrectomy.

Central pathology review

Of the 914 RCC cases diagnosed according to an original histopathological evaluation at each institution, 678 were classified as clear cell, 3 as multilocular clear, 49 as papillary, 51 as chromophobe, 1 as collecting ducts of Bellini, 1 as mucinous tubular and spindle, 24 as unclassified, 8 as other malignancy, 2 as oncocytoma, 3 as other benign, and 94 as undetermined according to the WHO classification (2004) through a

central pathology review. In 814 of the 914 RCC cases, RCC diagnosis was confirmed through a central pathological review, and clinical data were available. The patient and tumor characteristics are summarized in Table 1. Diagnoses made by the review board included clear cell RCC in 681 cases (83.7%), papillary RCC in 49 (6.0%; type 1 = 14, type 2 = 35), chromophobe RCC in 51 (6.3%), and unclassified RCC in 33 (4.1%) according to the Heidelberg RCC classification. Discordance of HS according to the Heidelberg RCC classification was identified in 66 of 729 cases with available original diagnoses (concordance rate 90.9 %; kappa = 0.555; 95% confidence interval (CI) 0.465–0.654; Table 2A). Twenty-three cases diagnosed as chromophobe RCC by central pathology review had originally been diagnosed as clear cell RCC. Considerable discordance in the nuclear grade following Japanese classification was identified in 569 of 721 cases with available original diagnoses (concordance rate 21.1%; kappa = -0.079; 95% CI -0.108–0.051; Table 2B). Two hundred and fifty-three and 100 cases diagnosed as G2 and G3 RCC by central pathology review had been originally diagnosed as G1. The overall concordance rate did not significantly differ among the institutions (P = 0.292).

HS and survival of RCC patients after potentially curative nephrectomy for local tumors

The 5- and 7-year OS rates of 814 RCC cases treated with curative nephrectomy were 92% and 87%, respectively (Fig. 1A), and the corresponding CSS and RFS rates were 96% and 93% and 88% and 85%, respectively (Fig. 1B and 1C). A total of 110 cases (93 clear, 6 papillary, 6 chromophobe, and 5 unclassified) from among 814 cases treated with curative nephrectomy experienced relapse during the follow-up period after curative nephrectomy. The 5-year CSS and RFS rates after curative nephrectomy among pT1N0M0, pT2N0M0, and pT3N0M0 cases in the present study were 99% and 96%, 93% and 80%, and 89% and 71%, respectively. Two hundred seventy-six cases received interferon-α as an adjuvant therapy. Interferon-α did not improve the OS (hazard ratio [HR] = 1.199; 95% CI, 0.839–1.714; P = 0.319), CSS (HR = 2.333; 95% CI, 1.405–3.874; P = 0.001), or RFS (HR = 2.428; 95% CI, 1.711–3.444; P <0.001) in the present study.

In a univariate analysis, OS was associated with HS in 5 subtypes: clear, papillary type 1, papillary type 2, chromophobe, and unclassified (P = 0.043) (Fig. 2A and Table 3); however, no association was found with the clear and

non-clear subtypes (P = 0.170, Fig. 2B). The lowest HR relative to the clear subtype was observed for chromophobe (0.62), followed by papillary type 1 (0.97), papillary type 2 (1.966), and unclassified subtype (2.426; Table 3).

OS was also associated with tumor size (P <0.001; Fig. 2C and Table 3), Fuhrman grade (P <0.001), gender (P = 0.005), PS (P <0.001), TNM stage (P <0.001), preoperative hemoglobin (Hb) level (P = 0.004), platelet (Plt) count (P = 0.003), albumin (alb) level (P <0.001), and C-reactive protein (CRP) level (P = 0.014), whereas CSS and RFS did not associate with age, PS, Hb, alb, or Plt (data not shown). The Fuhrman grade was a good prognostic factor for the clear (P <0.0001) and papillary histologic subtypes (P = 0.0389) but not the chromophobe subtype (P = 0.691), as previously described [12].

Additionally, we performed a multivariate analysis to identify the prognostic factors associated with OS, CSS, and RFS in RCC patients after potentially curative nephrectomy (Table 3). Hb, Plt, alb, and CRP were only available for approximately half of the patients and were therefore not included in this analysis. The multivariate analysis indicated that only tumor size, Fuhrman grade, and infiltration type were common independent

prognostic factors for OS, CSS, and RFS. Although gender was not directly related to age, female gender was a significantly good prognostic factor for OS ($P < 0.001$) but not for RFS ($P = 0.080$).

Discussion

We collected clinical data from 914 RCC patients treated with curative nephrectomy over a 6-year period beginning in 1995 and analyzed both clinical and histological data. The histological findings of these cases were reevaluated by 5 pathologists. Most previous large outcome studies required a study period longer than a decade or international collaborations between institutions with various backgrounds to collect sufficient numbers of patients. In contrast, the results from the current study appear to represent the true state of the art for RCC management during the era of the cytokine treatment for metastatic RCC (mRCC; circa 2000) in Japan.

The CSS rate in the present study appeared superior to those reported in Western countries, whereas the RFS rates were similar [13-16]. Fujii et al. also reported that the CSS among Japanese patients with RCC was longer than that reported in Western countries for patients with identical Mayo

Clinic stages, tumor sizes and grades, and necrosis (SSIGN) scores [17]. Naito et al. recently reported prolonged survival among mRCC patients in Japan when compared with those in Western countries during the era of cytokine treatment, suggesting that the lead time bias as a result of full medical tests and treatment coverage for all patients through the Japanese medical insurance system, genetic differences, or the use of non-recombinant interferon as an immunotherapy might have led to better prognoses [18]. Therefore, the long CSS in the present study might be the result of long survival of patients with metastatic RCC.

Several studies have reported better survival among female patients than among male patients after curative nephrectomy [19, 20]. In the present study, significantly better survival was observed among female patients with regard to OS but not RFS. A survival analysis adjusted for the estimated life expectancy would be necessary to understand the differences in RCC biological behavior between the genders.

The survival of RCC patients after curative nephrectomy did not significantly differ among the institutions after adjusting for gender, age, and tumor size ($P = 0.082$) and did not depend on the volumes of the

institutions. This is likely because most Japanese urologists (both residents in training and specialized urologists) experience multiple transitions between institutions, thus allowing the rapid transmission of surgical skills to all institutions, and because Japanese public medical insurance provides equal coverage to all hospitals in Japan.

Data for laparoscopic nephrectomy were limited and only available in 50 cases. This limitation reflects the policy of the Japanese public medical insurance system, which did not cover laparoscopic nephrectomy before 2002. However, local control of RCC via laparoscopic nephrectomy is comparable to that achieved via open nephrectomy [21] and is thus considered to be a reasonable method. Therefore, the results of the present study can be applied to localized RCC patients in current and future clinical settings.

Although Ficarra et al. reported a recent improvement in the concordance between the original and reviewing pathologists regarding RCC HS (kappa = 0.43 from 1986 to 1997; 0.73 from 1998 to 2000) [5], considerable discordance was identified in the present study with regard to HS (9.1%) and nuclear grade (78.9%). These increased discordance rates highlight the importance of a central pathological review, particularly for

series that include cases from more than a decade ago.

The prognostic significance of HS after curative nephrectomy was defined through univariate analysis [6-9, 22, 23]. Judging from the results of the present univariate analysis, patients with the chromophobe subtype had the best survival, followed by those with clear, papillary type 2, and unclassified subtypes; survival of papillary type 1 was almost equal to that of the clear subtype. However, whether HS is an independent prognostic factor remains under discussion. Leibovich et al. reported that HS was an independent predictor of outcome in a multivariate analysis of 3062 RCC patients from whom samples were collected between 1970 and 2003; in that study, all specimens were reviewed by a single pathologist [8]. Patard et al. reported that HS was not an independent prognostic factor in a multivariate analysis of 4204 RCC patients diagnosed between 1984 and 2001, but those authors described the lack of a central pathological review as the main limitation of their study [22]. Although Capitaneo et al. reported that HS was an independent predictor of cancer-specific mortality ($P = 0.03$), those authors found no improvement in accuracy when HS was added to other predictors [23]. Ficarra et al. reported that HS was not an

independent predictor of outcome in a multivariate analysis of 491 RCC patients from whom data were collected between 1986 and 2000, in which all specimens were reassigned by a single pathologist [5]. Amin et al. concluded that HS was not an independent predictor of outcome in a multivariate analysis of 405 RCC patients collected between 1968 and 1994, in which the final pathological review was performed by 3 pathologists [6]. Crepel et al. recently reported that HS was not a prognostic factor for the use of partial nephrectomy to treat small RCC [24]. Furthermore, even the unclassified subtype was not proven to be a statistically independent survival factor [25]. Although Keegan et al. reported that the HS was predictive of survival, only the rare collecting duct and sarcomatoid HS of RCC were definite independent survival factors [26]. The merit of the current study is the employment of a central pathological review according to the current WHO classification and the inclusion of RCC patients diagnosed between 1995 and 2000 with sufficient follow-up, indicating that it is among the most reliable RCC outcome studies in the era of cytokine treatment. In a multivariate analysis of the associations with OS, CSS, and RFS after potentially curative nephrectomy against local RCC in the

present study, HS was not found to be an independent prognostic factor even after the papillary subtype was further classified as type 1 or 2; additionally, a survival analysis of rare HS such as collecting duct carcinoma or sarcomatoid RCC was impossible because of the limited sample size. In contrast, tumor size, Fuhrman grade (excluding cases with the chromophobe subtype), and infiltration type had a much greater impact on survival after curative nephrectomy in the present study.

Certain potential limitations of the present study need to be considered. Despite analyzing a total of 814 RCC patients with available clinical and pathological evaluation data, the sample size was apparently not sufficiently large to determine statistical differences in survival among patients with different HS, including collecting duct HS and sarcomatoid HS. Moreover, although patients with RCC were consecutively enrolled in a retrospective manner, confirmation of the histopathological diagnosis of RCC in this study might have favored the selection of patients with resectable tumors. Therefore, a potential selection bias might have existed against patients with late-stage and rapidly growing disease. Finally, although central pathological reviews were performed by 5 specialized pathologists, only 2

representative H&E slides were available per case, resulting in 94 undetermined HS cases.

Despite some limitations, this report represents the true state of RCC outcomes via central pathological review near the year 2000. Although the RCC HS does not appear to be an independent prognostic factor after potentially curative nephrectomy, the prognostic significance of HS might increase after the emergence of targeting agents such as tyrosine-kinase inhibitors or mTOR inhibitors because some of these agents are designed to block the carcinogenic signaling pathways of specific RCC HS and therefore are more effective for these specific HS. It will be interesting to compare the significance of HS on RCC outcomes in the era of targeting agents with the present results.

In conclusion, the present study reported some of the most updated and reliable data regarding the survival of RCC patients treated with curative nephrectomy. HS was not an independent prognostic factor of RCC, whereas tumor size, Fuhrman grade (excluding chromophobe subtype cases), and infiltration type had much greater impacts on survival in the era of cytokine treatment. Considerable discordance between the original and

centrally reviewed pathological results regarding the HS and nuclear grades indicated that a central pathological review conducted by experienced pathologists in accordance with updated histopathological classifications is essential in large-scale outcome studies.

Acknowledgement

We thank Drs. F. Kono, Y. Kotani, T Manabe, and Y. Nagashima for participation in the central pathology review and Dr. M. Fukushima for study design. In addition, the authors thank Drs. T. Hayashi, Y. Nishio, K. Nishimura, Y. Taki, M. Nonomura, T. Hashimura, T. Matsuda, K. Ogura, H. Kanamaru, Y. Kakehi, A. Terai, M. Kawakita, M. Nishimura, H. Okuno, S. Fukuzawa, K. Okumura, Y. Shichiri, T. Ueda, H. Onishi, and H. Kinoshita for data collection. Support for this study was provided by Kyoto University, and partial support was provided by Pfizer, Inc. as Investigator-Initiated Research.

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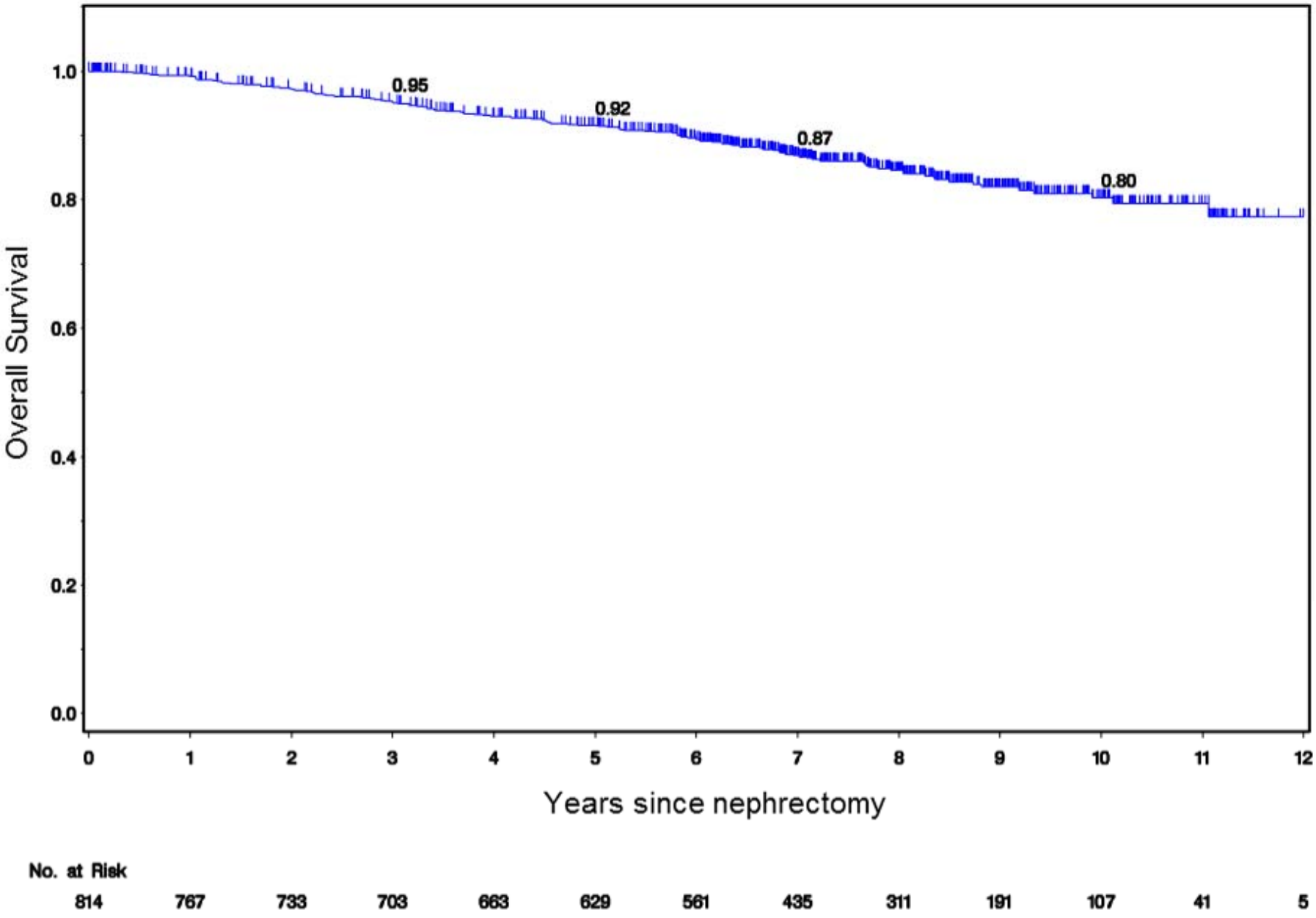
Figure legends

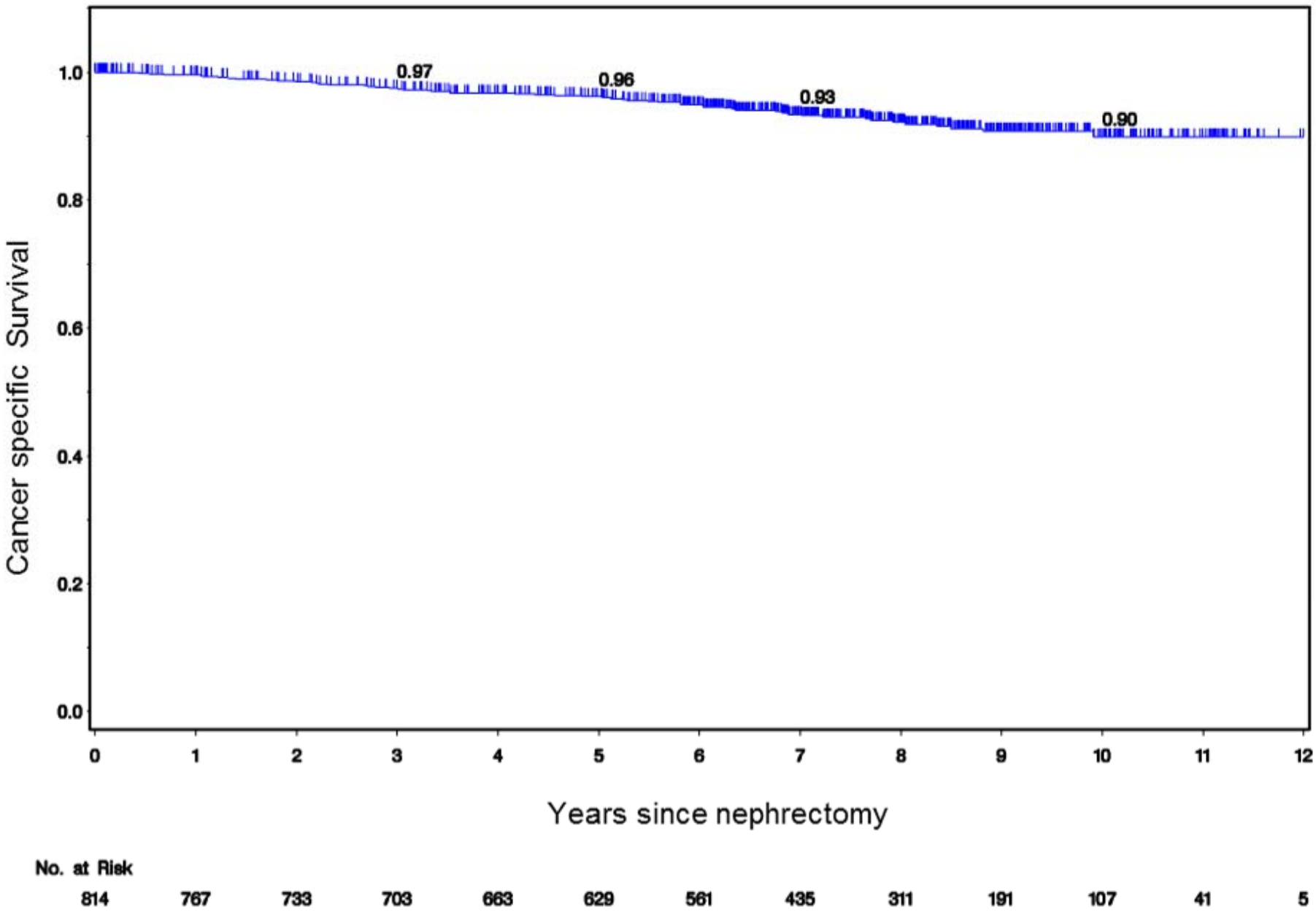
1. Overall survival (a), cancer-specific survival (b) and relapse-free survival (c) of 814 patients subjected to curative nephrectomy and central pathological diagnosis.

2. Overall survival stratification according to the 5 histologic subtypes (clear, papillary type 1, papillary type 2, chromophobe, and unclassified) (a), clear vs. non-clear subtypes (b), and tumor size (c) among 814 patients subjected to curative nephrectomy and central pathological diagnosis.

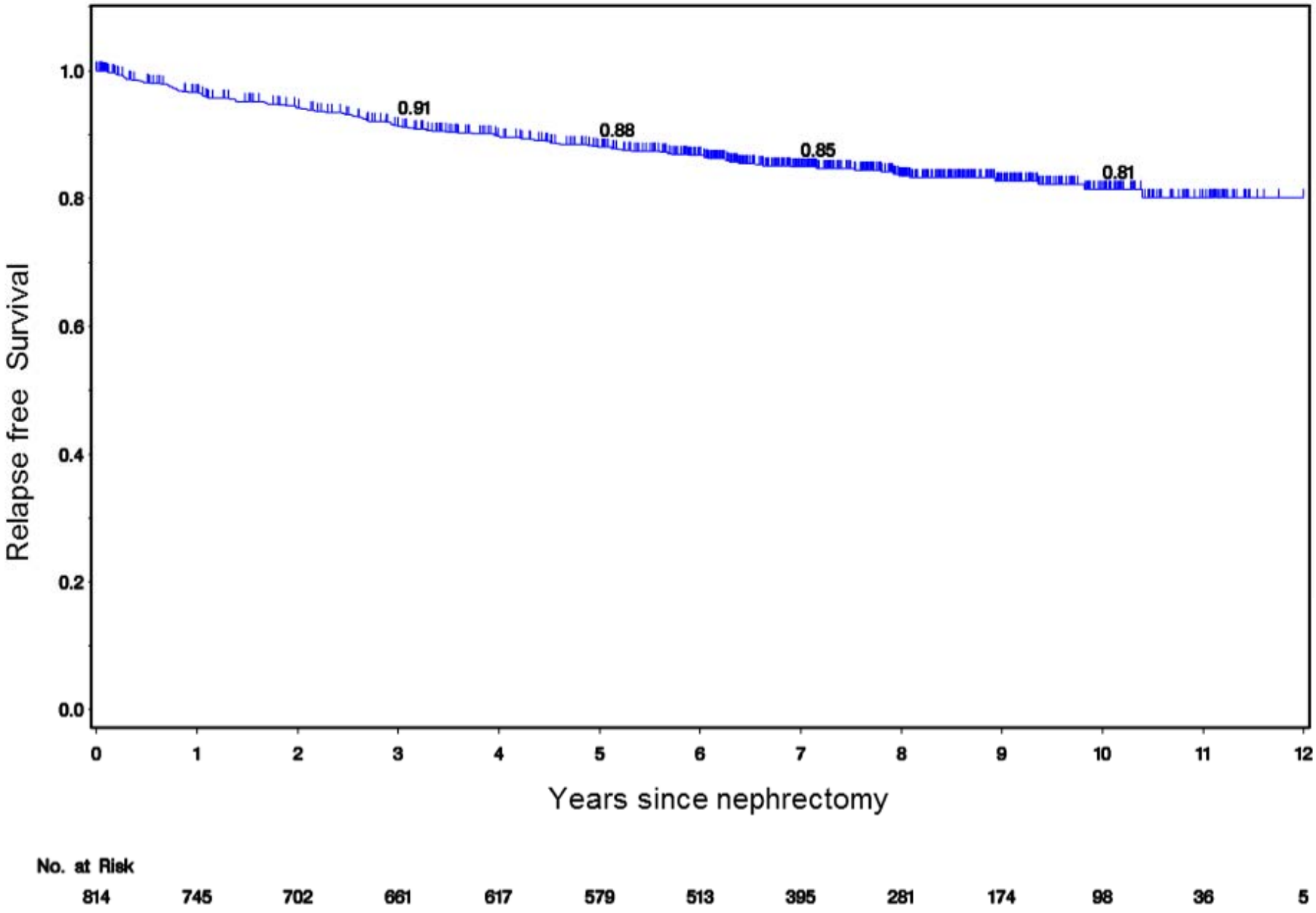
1 (a)


Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.95
0.92
0.87
0.80
0
1
2
3
4
5
6
7
8
9
10
11
12
Years since nephrectomy
No. at Risk
814
767
733
703
663
629
561
435
311
191
107
41
5

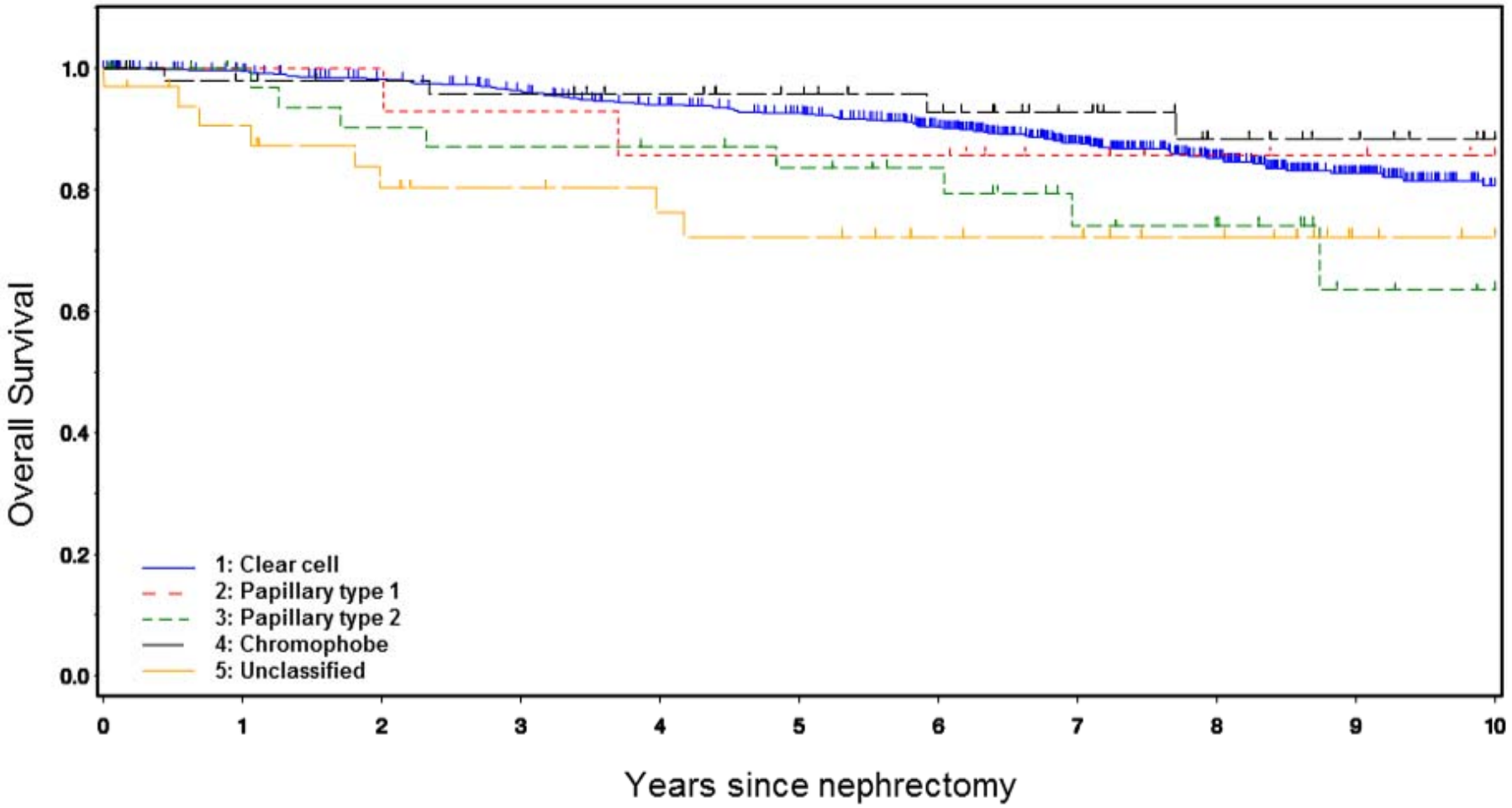
1 (b)


Cancer specific Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.97
0.96
0.93
0.90
0
1
2
3
4
5
6
7
8
9
10
11
12
Years since nephrectomy
No. at Risk
814
767
733
703
663
629
561
435
311
191
107
41
5

1 (c)

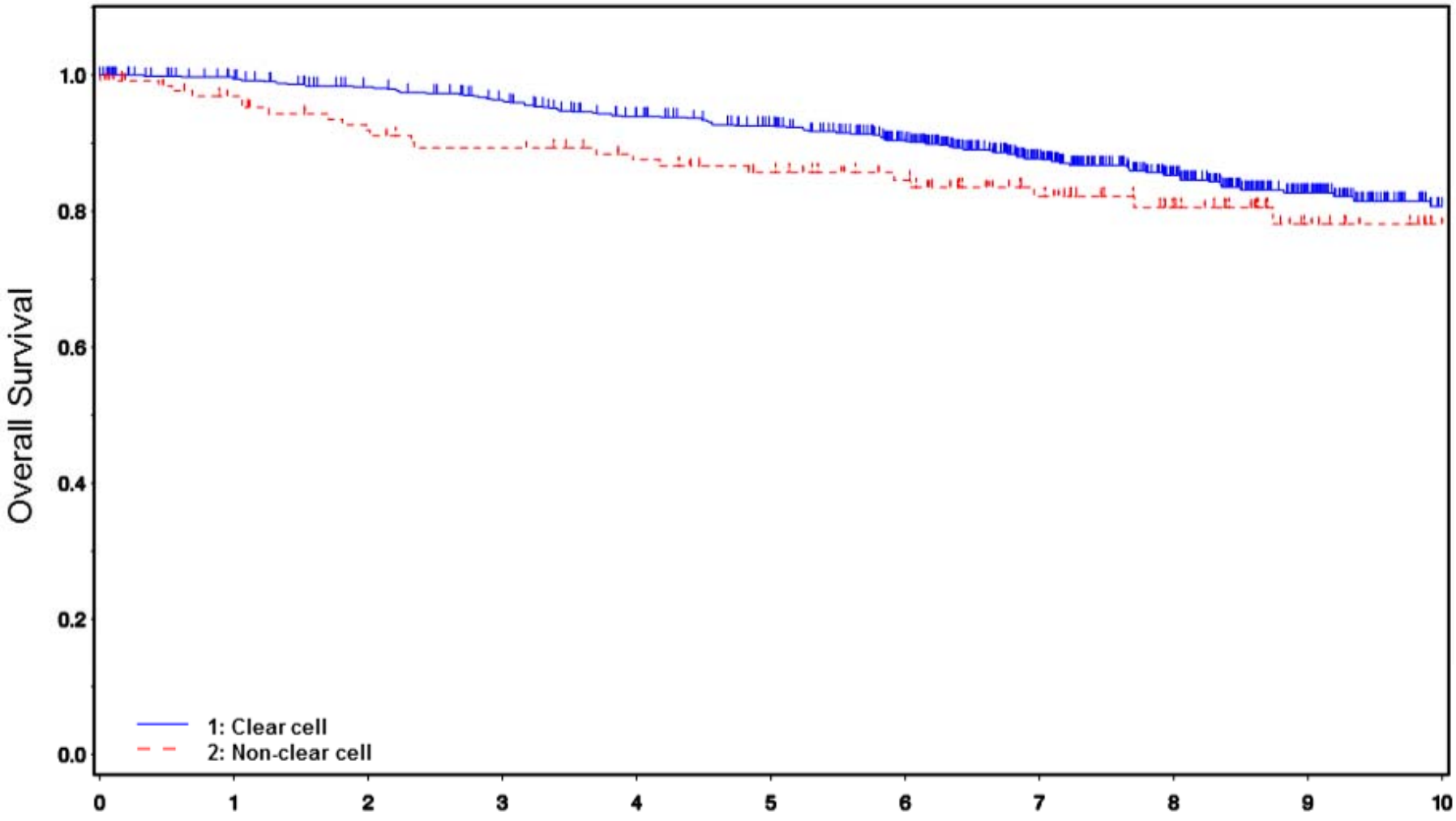

Relapse free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.91
0.88
0.85
0.81
0
1
2
3
4
5
6
7
8
9
10
11
12
Years since nephrectomy
No. at Risk
814
745
702
661
617
579
513
395
281
174
98
36
5

2 (a)



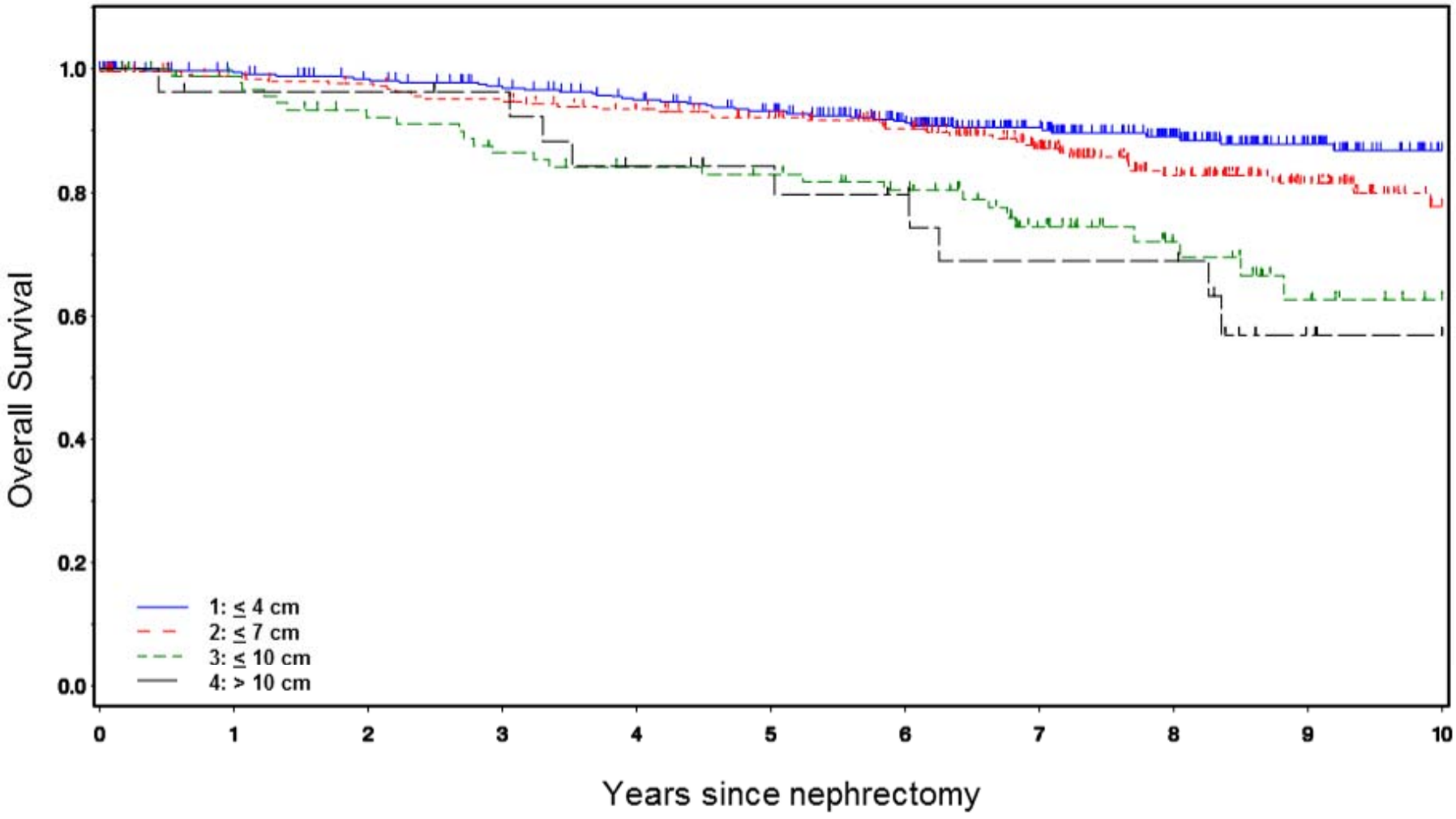
No. at Risk											
1	681	648	624	599	566	540	482	374	265	164	92
2	14	14	14	13	12	12	12	8	6	5	3
3	35	31	28	27	26	23	20	14	12	5	3
4	51	46	44	43	40	36	32	25	17	13	7
5	33	28	23	21	19	18	15	14	11	4	2

2 (b)



No. at Risk											
1	681	648	624	599	566	540	482	374	265	164	92
2	133	119	109	104	97	89	79	61	46	27	15

2 (c)



No. at Risk											
1	389	368	355	339	323	308	270	211	153	99	60
2	261	245	239	232	219	206	188	149	101	62	32
3	96	89	80	74	70	68	62	42	27	16	8
4	27	25	25	24	20	18	16	13	13	5	3

Table 1

Descriptive characteristics of 814 renal cell carcinoma (RCC) patients with curative nephrectomy for whom both clinical data and a central pathological review were available, stratified by histological subtype (HS) according to the Heidelberg Classification and the descriptions of types 1 and 2 papillary RCC (percentages in parentheses)

Characteristic	Clear Cell	Papillary (Type 1)	Papillary (Type 2)	Chromophobe	Unclassified	P*
Patients	681 (83.7)	14 (1.7)	35 (4.3)	51 (6.3)	33(4.1)	
Gender						
M	496 (72.8)	12 (85.7)	30 (85.7)	25 (49.0)	19 (57.6)	0.0003
F	185 (27.2)	2 (14.3)	5 (14.3)	26 (51.0)	14(42.4)	
Age (years)						
Mean ± SD	60.9 ± 11.3	65.1 ± 10.4	65.6 ± 9.7	60 ± 10.5	61.9± 12.8	0.082
Performance Status						
0	491 (89.1)	11 (84.6)	28 (87.5)	40 (93.0)	23 (85.2)	0.835
1–4	60 (10.9)	2 (15.4)	4 (12.5)	3 (7.0)	4 (14.8)	
BMI						
Mean ± SD	23.2 ± 3.3	21.8 ± 2.0	22.5± 3.2	23.9 ± 3.2	22.1 ± 3.6	0.067
Clinical presentation						
Incidental	508 (74.9)	11 (78.6)	24 (68.6)	36 (70.6)	19 (59.4)	0.306
Symptomatic	170 (25.1)	3 (21.4)	11 (31.4)	15 (29.4)	13 (40.6)	
Tumor size (cm)						
Mean ± SD	4.8 ± 2.7	5.3± 2.3	4.3 ± 2.7	5.5 ± 3	4.9 ± 1.9	0.273
T stage						
1a/1b/2a/2b	580 (88.8)	13 (92.9)	28 (82.4)	45 (95.7)	26 (83.9)	0.320
3a/3b/3c/4	73 (11.2)	1 (7.1)	6 (17.6)	2 (4.3)	5 (16.1)	
Hb (g/dL)						
Mean ± SD	13.5 ± 1.9	13.5 ± 1.3	13.1 ± 2.0	13.4 ± 1.8	12.0 ± 2.2	0.0005
Plt (10^4/mm^3)						
Mean ± SD	25.7± 22.4	22.4 + 6.1	24.4 ± 9.5	22.9 ± 6.9	26.7 ± 8.7	0.878
LDH (IU/L)						
Mean ± SD	271.5 ± 105.3	371.3± 309.8	296.5 ± 135	351 ± 108	282.2 ± 117.6	0.0001
Alb (g/dL)						
Mean ± SD	4.2 ± 0.6	4.2 ± 0.7	4.0 ± 0.4	4.2 ± 0.8	4.1 ± 0.7	0.583
Corrected Ca (mg/dL)						
Mean ± SD	8.1 ± 2.3	8.9 ± 0.4	8.5 ± 1.8	8.9 ± 2.2	7.5 ± 2.7	0.096
CRP (mg/dL)						
Mean ± SD	1.0 ± 3.0	0.2 ± 0.1	2.3 ± 4.7	0.6 ± 2.1	1.8 ± 3.2	0.165
Infiltration						
INF α	399 (81.4)	8 (80.0)	19 (70.4)	31 (79.5)	18 (64.3)	0.164
INF β/INF γ	91 (18.6)	2 (20.0)	8 (29.6)	8 (20.5)	10 (35.7)	
Venous invasion						
v(-)	393 (77.8)	9 (81.8)	17 (70.8)	31 (88.6)	19 (70.4)	0.406
v(+)	112 (22.2)	2 (18.2)	7 (29.2)	4 (11.4)	8 (29.6)	
Fuhrman grade						
G1/G2	436 (64.0)	10 (71.4)	13 (37.1)	9 (17.6)	6 (24.0)	0.0001
G3/G4	245 (36.0)	4 (28.6)	22 (62.9)	42 (82.4)	19 (76.0)	

*** Chi-squared test for categorical variables and ANOVA for continuous variables.**

SD, standard deviation; BMI, body mass index; Hb, hemoglobin; Plt, platelet count; LDH, lactate dehydrogenase; Alb, albumin; Ca, calcium; CRP, C-reactive protein; INF, infiltration

Table 2

Concordance of histological subtypes (a) and nuclear grade (b) between original and centrally reviewed pathology results

A

	Central pathology review			
	clear	papillary	chromophobe	unclassified
Original histological subtype				
clear	**620**	**5**	**23**	**13**
papillary	**10**	**31**	**0**	**6**
chromophobe	**1**	**0**	**11**	**0**
unclassified	**6**	**2**	**0**	**1**

Concordance rate = 90.9%; kappa = 0.555; 95% confidence interval (CI), 0.465–0.654

B

	Central pathology review		
	G1	G2	G3
Original nuclear grade			
G1	**6**	**253**	**100**
G2	**4**	**125**	**211**
G3	**0**	**1**	**21**

Concordance rate = 21.1%; kappa = -0.079; 95% confidence interval (CI), -0.108–0.051

Table 3
Univariate and multivariate analyses of prognostic factors for survival after curative nephrectomy

		OS					CSS	RFS
		Univariate				Multivariate	Multivariate	Multivariate
		HR	95% CI	P	P*	P*	P*	P*
Gender	M	1			0.005	<0.001	0.048	0.069
	F	0.500	0.309–0.811	0.005				
Age		1.045	1.025–1.064	<0.001	<0.001	<0.001	0.391	0.097
Hemodialysis	-	1			<0.001	<0.001	0.061	0.638
	+	5.434	1.998–14.78	<0.001				
Performance status	0	1	—	—	<0.001	<0.001	0.903	0.486
	1	3.045	1.805–5.138	<0.001				
	2–4	7.161	2.868–17.88	<0.001				
Tumor size		1.162	1.105–1.221	<0.001	<0.001	<0.001	<0.001	<0.001
T stage	1a	1			<0.001	0.305	0.015	0.001
	1b	1.325	0.760–2.309	0.321				
	2	2.215	1.143–4.291	0.018				
	3a	2.454	1.350–4.462	0.003				
	3b	4.503	2.474–8.99	<0.001				
	3c	9.901	3.026–32.40	<0.001				
	4	14.17	1.903–105.5	0.010				
Infiltration type	INF α	1			<0.001	0.016	0.001	<0.001
	INF β	2.167	1.362–3.448	0.001				
	INF γ	13.06	4.059–42.02	<0.001				
Venous invasion	-	1			<0.001	0.232	0.335	0.777
	+	3.087	2.037–4.680	<0.001				
Fuhrman grade	1/2	1			<0.001	0.005	<0.001	0.002
	3	2.470	1.640–3.720	<0.001				
	4	2.236	1.305-3.830	0.003				
Histological subtype	clear	1			0.043	0.714	0.499	0.999
	papillary type 1	0.970	0.239–3.937	0.966				
	papillary type 2	1.966	0.954–4.051	0.067				
	chromophobe	0.620	0.228–1.686	0.349				
	unclassified	2.426	1.177–5.000	0.016				

* Global association
OS, overall survival; CSS, cancer-specific survival; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; INF, infiltration